DETAILED ACTION

Status of the Claims

Claim(s) 1-31 are pending. Claim(s) 1-9 are under examination. The following Office Action is in response to Applicant's communication dated November 12, 2009.

Examiner of Record

As an initial matter, it is noted that the examiner of record has been changed from Suchira Pande, Art Unit 1637, to Christopher M. Babic, Art Unit 1637.

Drawings

The replacement drawings were received on November 12, 2009. These drawings are acceptable.

Election/Restrictions

In response to the request to withdrawal the restriction requirement issued March 31, 2009, Applicant is respectfully reminded that the restriction requirement was made FINAL in the NON-FINAL Office Action dated August 11, 2009.

Claim Rejections - 35 USC § 112 - Indefiniteness - Withdrawn

Applicant's claim amendments are sufficient to overcome the rejection of claim(s) 1-9 presented in the Office Action dated August 11, 2009. Thus, the rejection has been withdrawn.

Claim Rejections - 35 USC § 102 - Withdrawn

Applicant's claim amendments and supplemental remarks are sufficient to overcome the rejection of claim(s) 1-3, 5, and 7 over de Sauvage. Thus, the rejection has been withdrawn.

Claim Rejections - 35 USC § 103 - New Grounds

The following new grounds of rejection is presented in view of Applicant's amendments.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

1. Claims 1, 2, and 4-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Danenberg et al. (U.S. 6,582,919 B2) in view of GENBANK Accession No. NM_004448 (May 7, 1999), in view of Buck et al ("Design Strategies and Performance of Custom DNA Sequencing Primers" Biotechniques. 1999. 27(3): pages 528-536), and in further view of Lowe et al. (Nucleic Acids Research, Vol. 18, No. 7, page 1757-1761, 1990).

Danenberg teaches real-time PCR amplification utilizing the primers and probes depicted below for detection of a HER2 target sequence (examples 1,2, for example).

EGFR-1773: ACGCATTCCCTGCCTCGGCTG;
HER2-neu 2657: TGTGTACGAGCCGCACATCCTCCA; or
beta-actin-611: ACCACCACGGCCGAGCGG;
EGFR-1753F: TGCGTCTCTTGCCGGAAT;
EGFR-1823R: GGCTCACCCTCCAGAAGCTT;
HER2-neu 2671F: CTGAACTGGTGTATGCAGATTGC;
HER2-neu 2699R: TTCCGAGCGGCCAAGTC;
beta-actin-952F: TGAGCGCGGCTACAGCTT; and
beta-actin-651R TCCTTAATGTCACGCACGATTT.

Danenberg does not specifically teach the primer sequences recited in SEQ ID NOs: 7, 8, or 12.

However, it is first noted that the HER2 target sequence, the sequence from which the claimed oligonucleotides were derived, is a sequence that was well known at

the time of invention (see GENBANK Accession Nos. NM_004448 as well as pg. 9 of Applicant's disclosure). Thus, the binding site of SEQ ID NOs: 7 for example is suggested within the sequence disclosed by NM_004448 (see alignment of NM_004448 with SEQ ID NO: 7 for example below).

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                2530        2540        2550        2560        2570        2580
232862  ACATCCACGGTGCAGCTGGTGACACAGCTTATGCCCTATGGCTGCCTCTTAGACCATGTC

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                2590        2600        2610        2620        2630        2640
232862  CGGGAAAACCGCGGACGCCTGGGCTCCCAGGACCTGCTGAACTGGTGTATGCAGATTGCC
                                                    ::::::::::::::::::::::
_       ------------------------------------------CTGAACTGGTGTATGCAGATTGC-
                                                          10          20

                2650        2660        2670        2680        2690        2700
232862  AAGGGGATGAGCTACCTGGAGGATGTGCGGCTCGTACACAGGGACTTGGCCGCTCGGAAC

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Applicant is directed to *In Re Deuel* 34 USPQ 2d 1210 (Fed. Cir. 1995), the Court of Appeals for the Federal Circuit determined that the existence of a general method of identifying a specific DNA does not make the specific DNA obvious. Regarding structural or functional homologs, however, the Court stated,

"Normally, a *prima facie* case of obviousness is based upon structural similarity, i.e., an established structural relationship between a prior art compound and the claimed compound. Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologs because homologs often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties."

Since the claimed sequences simply represent structural homologs of those sequences disclosed in the prior art, and concerning which a biochemist of ordinary skill

would attempt to obtain alternate compounds with improved properties, the claimed primers and probes (SEQ ID NOs: 7, 8, and 12) is *prima facie* obvious over the cited references in the absence of secondary considerations.

Buck provides a supporting disclosure that expressly presents evidence of the equivalence of primers. Specifically, Buck invited primer submissions from a number of labs (39) (page 532, column 3), with 69 different primers being submitted (see page 530, column 1). Buck also tested 95 primers spaced at 3 nucleotide intervals along the entire sequence at issue, thereby testing more than 1/3 of all possible 18 mer primers on the 300 base pair sequence (see page 530, column 1). When Buck tested each of the primers selected by the methods of the different labs, Buck found that EVERY SINGLE PRIMER worked (see page 533, column 1). Only one primer ever failed, No. 8, and that primer functioned when repeated. Further, EVERY SINGLE CONTROL PRIMER functioned as well (see page 533, column 1). Buck expressly states "The results of the empirical sequencing analysis were surprising in that nearly all of the primers yielded data of extremely high quality (page 535, column 2)." Therefore, Buck provides direct evidence that all primers would be expected to function, and in particular, all primers selected according to the ordinary criteria, however different, used by 39 different laboratories. It is particularly striking that all 95 control primers functioned, which represent 1/3 of all possible primers in the target region. This clearly shows that every primer would have a reasonable expectation of success.

In addition to teachings of Buck, Lowe provides a supportive disclosure that teaches a method for designing primers and evaluating their performance wherein a

computer program is used for rapid selection of oligonucleotide primers for polymerase chain reaction (see page 1757, col. 1, abstract). The reference teaches that all primers designed for over 10 gene products were experimentally tested and the results showed that all the amplification products specified by the primers are of the predicted size and also hybridize with the appropriate cDNA or internal oligonucleotide probe (see page 1760, col. 2, paragraph 1).

As explained above, the claimed sequences simply represent structural homologs of those sequences disclosed in the prior art, and concerning which a biochemist of ordinary skill would attempt to obtain alternate compounds with improved properties, the claimed primers and probe (SEQ ID NOs: 1, 2, and/or 3) are *prima facie* obvious over the cited references in the absence of secondary considerations.

Furthermore, it would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention, to combine the known HER2 nucleic acid sequences as taught by the prior art with a step of generating and designing primers as taught by Lowe to measure the expression of HER2 because such genomic sequences were known (Danenberg and GENBANK) at the time the invention was made, and it is obvious to generate primers from known sequences as taught by Lowe. The ordinary artisan would have had a reasonable expectation of success that such primers or primer pairs generated using known sequences as taught by GENBANK in view of Lowe to amplify HER2 sequences for detection because the claimed primers are functional equivalents of the sequences taught by Danenberg and Lowe explicitly taught that all primers designed for over 10 gene products were experimentally tested and the results

showed that all the amplification products specified by the primers are of the predicted size (see page 1760, col. 2, paragraph 1). The ordinary artisan would have been motivated to generate a number of said primers and primer pairs for detection of KPC sequences to provide flexibility and optimize experimentation. Selection of specific oligonucleotides for specific T_m represents routine optimization with regard to sequence, length and composition of the oligonucleotide. Such optimization parameters are explicitly recognized in Lowe (This clearly shows that every primer would have a reasonable expectation of success). As noted in *In re Aller*, 105 USPQ 233 at 235, more particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation. Routine optimization is not considered inventive and no evidence has been presented that the primer selection performed was other than routine, that the products resulting from the optimization have any unexpected properties, or that the results should be considered unexpected in any way as compared to the closest prior art.

It is noted that a sufficient showing of a secondary consideration (e.g. unexpected results) would obviate this and any further rejection of this type.

2. Claim 3 is rejected under 35 U.S.C. 103(a) as being unpatentable over Danenberg et al. (U.S. 6,582,919 B2) in view of GENBANK Accession No. NM_004448 (May 7, 1999), in view of Buck et al ("Design Strategies and Performance of Custom DNA Sequencing Primers" Biotechniques. 1999. 27(3): pages 528-536), in view of Lowe et al. (Nucleic Acids Research, Vol. 18, No. 7,

page 1757-1761, 1990) as applied to claim 1 above, and in further view of Van Gelder et al. (U.S. 5,545,522).

The teachings of the previously applied reference(s) have been outlined in the above rejections. The previously applied reference(s) do not expressly teach primers comprising a T7 transcription promoter.

Van Gelder provides a supportive disclosure that teaches the addition of a T7 promoter sequence to a primer for the purpose of creating aRNA subsequent to DNA amplification (fig. 1; col. 4, lines 40-end, for example).

Thus, in summary, it is submitted that it would have been *prima facie* obvious to a person of ordinary skill in the art at the time of invention to incorporate a T7 promoter sequence to the primers of Dananberg since Van Gelder suggests such a modification to allow for downstream aRNA production.

3. Claims 8 and 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Danenberg et al. (U.S. 6,582,919 B2) in view of GENBANK Accession No. NM_004448 (May 7, 1999), in view of Buck et al. ("Design Strategies and Performance of Custom DNA Sequencing Primers" Biotechniques. 1999. 27(3): pages 528-536), in view of Lowe et al. (Nucleic Acids Research, Vol. 18, No. 7, page 1757-1761, 1990) as applied to claim 1 above, and in further view of Spik et al. ((1991) J. Biol. Chem. 266 917): pp10735-10738).

Regarding claim 8, de Sauvage et al. teach method of claim 7, but do not explicitly teach wherein one of the amplification primers for obtaining amplicons specific to a housekeeping gene comprises at least 15 nucleotide motifs of a sequence selected from SEQ ID No. 25 to 29.

Regarding claim 8, Spik et al. teach wherein one of the amplification primers for obtaining amplicons specific to a housekeeping gene comprises at least 15 nucleotide motifs of a sequence selected from SEQ ID No. 25 to 29 (See page 10736 Fig. 2 nt 264 to 283 of SCYLP sequence correspond to nt 1-20 of primer recited as SEQ ID 28 in instant application. See alignment below:

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RESULT 1
264to283

  Query Match             100.0%;  Score 105;  DB 1;  Length 20;
  Best Local Similarity   100.0%;  Pred. No. 0;
  Matches   20;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps
0;

Qy          1 AGGAGAGAAAGGATTTGGCT 20 SEQ ID NO 28
              ||||||||||||||||||||
Db          1 AGGAGAGAAAGGATTTGGCT 20 Region of SCYLP sequence (nt 264-283)
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Thus by teaching a 100% match to a 20 mer region comprised in a bigger region Spik et al. teach wherein one of the amplification primers for obtaining amplicons specific to a housekeeping gene comprises at least 15 nucleotide motifs of SEQ ID No. 28.

Regarding claim 9, Spik et al. teach first amplification primer comprising at least 15 nucleotide motifs of nucleotide sequence SEQ ID No. 27 (page 10736 Fig. 2 nt 503 to 482 of SCYLP sequence correspond to nt 1-22 of primer recited as SEQ ID 27 in instant application. See alignment below

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RESULT 1
482to503/c

  Query Match             100.0%;  Score 134;  DB 2;  Length 22;
  Best Local Similarity   100.0%;  Pred. No. 0;
  Matches   22;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps
0;

Qy          1 CAGGCTGTCTTGACTGTCGTGA 22 SEQ ID 27
              ||||||||||||||||||||||
Db         22 CAGGCTGTCTTGACTGTCGTGA 1  Region of SCYLP
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Thus by teaching a 100% match to a 22 mer region comprised in a bigger region Spik et al. teach first amplification primer comprising at least 15 nucleotide motifs of nucleotide sequence SEQ ID No. 27

Regarding claim 9, Spik et al. teach a second amplification primer comprising at least 15 nucleotide motifs of nucleotide sequence SEQ ID No. 28. See details provided above for location on SCYLP sequence where SEQ ID NO 28 binds.

Thus primer of SEQ ID NO 28 will act as upstream 5' end primer and primer of SEQ ID NO 27 will act as downstream 3' end primer to amplify ~240 bp amplicon from the SCYLP sequence.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to design primers using the SCYLP gene sequence taught by Spik et al. to amplify a housekeeping gene. SCYLP is a gene whose product is expressed in human milk. In other words this gene SCYLP is expressed in mammary tissue. One of ordinary skill in the art is taught by Spik et al. that the central part of the SCYLP molecule corresponds to highly conserved part of the amino acids (see page 10737 col. 2 top 4 lines). Hence one of ordinary skill in the art has a reasonable expectation of success in being able to amplify a ~240 bp amplicon using the above two

primers which are designed from the conserved region of SCYLP gene. Since breast cancer cells are also derived from mammary tissue, the choice of a housekeeping gene that is also expressed in mammary tissue provides for a good internal control.

Conclusion

No claims are allowed.

The prior art made of record and not relied upon is considered pertinent to Applicant's disclosure:

Gelmini et al. (Clin Chem. 1997 May;43(5):752-8); teaches real-time PCR amplification of HER2.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the

shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christopher M. Babic whose telephone number is 814-880-9945. The examiner can normally be reached on Monday-Friday 10:00AM to 6:00PM EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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